Desymmetrization Reactions: A Convenient Synthesis of Aromatic Diamide Diamines

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Abstract: A two-step process for the synthesis of various diamide diamines derived from 1,n-diamino benzene compounds is described. The amidation reaction is simple, mild, involves readily available bis(*N*-acylthiazolidine-2-thione) derivatives as acylating agents and requires only stoichiometric equivalents of diamine and acylating agents.

Key words: regioselectivity, aromatic diamines, acylation, diamides, *N*-acylthiazolidine-2-thione

Aromatic diamide diamines are useful precursors for the synthesis of several classes of compounds, which are widely used in host guest chemistry for the selective recognition of metal ions or neutral molecules. Applications of these building blocks include bis(benzimidazoyl) and diamide diimide derivatives[2,3] or dissymetrical tetraamides and tetralactams.[4,5] They are also key intermediates for the access to amide-based catenanes.[6] Aromatic diamide diamines themselves have been also tested as drug candidates,[7] ion chelating agents[8] or in asymmetric synthesis.[9]

The preparation of such compounds involves a strategy based on the formation of amide bonds and on the differentiation of two chemically equivalent aromatic amino groups. Amide bonds are generally formed quite simply via the reaction of an activated acid with an amine,[10] but direct monoacylation of symmetrical diamines is frequently complicated by the tendency to bis-acylation side reaction. The utilization of stoichiometric equivalents of an aromatic diamine and a diacid derivative usually generates a mixture of the diamide diamine compound, cyclic (polylactams) and polymeric products. To date this pitfall has been circumvented most easily by employing a large excess of the starting diamine relative to the acylating agent.[4–6,8a] However, the low volatility of aromatic diamines makes the separation of the diamide diamine product from unreacted diamine troublesome. Two indirect, multistep methods have been also described to obtain this family of compounds. They involve the use of a nitroaromatic amine, followed by reduction of the nitro group,[2a–c,11] or the selective monoprotection of one nitrogen atom of the diamine, followed by acylation of the remaining nitrogen and finally deprotection.[12]

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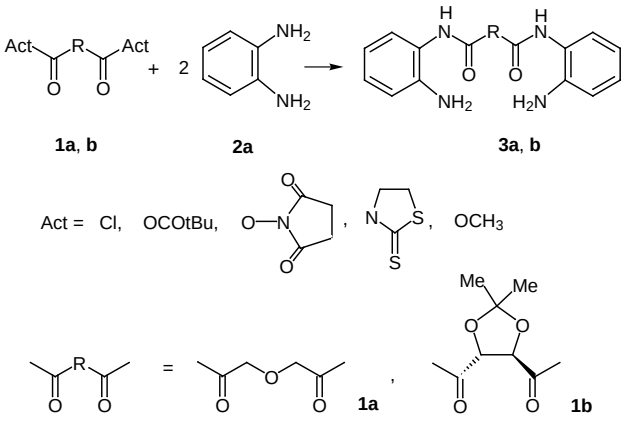


Scheme 1

Here we report a simple and mild method, which produces aromatic diamide diamines in good yields even when stoichiometric equivalents of diamine and activated diacid are utilized. This procedure allows the efficient use of a diamine without resorting to costly and time-consuming procedures. Preliminary results of this work have been previously published.[13]

In connection with our studies directed towards the synthesis of macrocyclic polylactams,[14] we needed an efficient method for the access to diamide diamines **3a**,**b** derived from 1,2-diaminobenzene and diglycolic acid or 2,3-*O*-isopropylidene-L-tartaric acid respectively (Scheme 1). In studies on the reaction of symmetrical aliphatic diamines with iso(thio)cyanates[15] or activated acids,[16] it has been shown that a decrease of the reactivity of the electrophilic reagent leads to increased yields in mono-substituted diamines. Thus, we carried out a study in order to compare the yield of diamide diamines **3a**,**b** as a function of the reactivity of the acylating group (Table 1).

Table 1 Comparison of the Yield (%) of Diamide Diamines **3a**,**b** from the Reaction of 1,2-Diaminobenzene with Various Acylating Agents[a] Derived from **1** (Scheme 1)

Act	Cl	OCOBu-*t*	OSu	TT	OMe
3a	20	29	0 (79)[b]	80	0
3b	18	24	0 (75)[b]	60	0

[a] Abbreviations used: Su = succinimide, TT = 1,3-thiazolidine-2-thione.
[b] Yield of bis(benzimidazolyl) product (See Figure).

Table 2 Preparation of Diamide Diamines **3a**–**u**[a]

Entry	Reagents		Diamide Diamine **3**[b]	
	1	**2**	Yield (%)[c]	mp (°C)[d]
a	**1a**	**2a**	80 (93)[e]	169–170
b	**1b**	**2a**	60	168–169
c	**1c**	**2a**	87	208–210
d	**1d**	**2a**	94	189–190
e	**1e**	**2a**	92	164–165
f	**1f**	**2a**	70	158–159
g	**1g**	**2a**	52	216–218
h	**1h**	**2a**	68	228–230
i	**1i**	**2a**	91	236–237
j	**1j**	**2a**	57 (75)[e]	200–201
k	**1k**	**2a**	81	193–194
l	**1a**	**2b**	59[f]	192–193
m	**1a**	**2c**	63[f]	171–173
n	**1a**	**2d**	46[f]	163–165
o	**1a**	**2e**	55[f]	213–214
p	**1a**	**2f**	45	175–177
q	**1i**	**2f**	69	236–238
r	**1a**	**2g**	98[f]	154–156
s	**1a**	**2h**	90	amorphous solid
t	**1i**	**2h**	98	218–219
u	**1a**	**2i**	91[f]	134–135

[a] Reactions conditions: mercaptothiazolide (1 equiv), diamine (2 equiv), CH_2Cl_2 as solvent except for **3n** (DMF) and **3o** (MeCN).
[b] The alphabets **a**–**u** in the entry correspond to the numbering of the products **3a**–**u**. Elemental analysis (C, H, N) calculated and found values were within ± 0.4% for all compounds **3** except for **3n** (H, 0.49) and **3r** (C, 0.45).
[c] Refers to isolated product.
[d] Recrystallization solvent: MeCN.
[e] Reactions conditions: mercaptothiazolide (1 equiv), diamine (3 equiv).
[f] For compounds **3l**,**m**,**r** the methyl, chloro, or fluoro substituents are in the 4,4' position. For compound **3o** the methoxycarbonyl substituents are in the 5,5' position. For compound **3u** the methyl substituents are in the 3,3' position.

The reaction of diacid dichlorides **1a**,**b** (Act = Cl) with two equivalents of 1,2-diaminobenzene in anhydrous THF in the presence of triethylamine afforded the corresponding diamide diamines **3a**,**b** after aqueous workup and column chromatography in ~20% yield. Substitution of an anhydride group for a chloro group in the diacid dichloride (mixed pivalic anhydride activation) gave also poor yields of the target products. The procedure involving *N*-hydroxysuccinimide (HOSu) active esters, commonly used in peptide chemistry, has been reported to be successful in the monoacylation of symmetrical aliphatic diamines,[16] but unsuccessful when 1,2-diaminobenzene was used. Efforts to synthesize **3a**,**b** via the hydroxysuccinimide route were thwarted by the exclusive formation (yields greater than 75%) of bis(benzimidazolyl) derivatives (Figure). It should be noted that this reaction takes place smoothly at room temperature, in sharp contrast with other methodologies[17] used for the preparation of such compounds. Acylation was also attempted with less active reagents, such as dimethyl esters. These esters are known to react with aliphatic diamines,[18] but owing to the lesser nucleophilicity of the aromatic diamine, no reaction occurred in these experiments, even after long reaction time. Finally, the solution to the synthesis of diamide diamines **3a**,**b** was found by the activation of the diacid as a bis(2-mercaptothiazolide). As a matter of fact, acids activated with 1,3-thiazolidine-2-thione (TTH) react smoothly with aromatic amines,[19] their reactivity being much lower than that of succinimide esters and higher than that of methyl esters. Furthermore, these acylating agents are stable and easy to handle in the open atmosphere at room temperature, and form after aminolysis a stable byproduct; the 1,3-thiazolidine-2-thione that will not induce salts formation or side reactions. Reactions were carried out at room temperature in dichloromethane by addition of mercaptothiazolides **1a**,**b** to two equivalents of 1,2-diaminobenzene. The target compounds **3a**,**b** were isolated by a simple filtration of the reaction mixture (**3a**) or by chromatography on silica gel (**3b**) with 80% and 60% yield, respectively. It should be noted that the higher yield observed with **3a** does not reside in its precipitation from the solution when it is formed (releasing it out of competition from acylating agent). Similar yield was observed when a better dissolving medium (DMF) was used.

In order to demonstrate the easy access of the starting acylating agents and to explore the usefulness of this method, the selective functionalization of 1,2 diaminobenzene with nine different bis(mercaptothiazolide) derivatives was examined (Scheme 2 and Table 2, entries **c**–**k**). Acylthiazolidinethiones may be prepared by the reaction of 1,3-thiazolidine-2-thione with the carboxylic acid, in the presence of (i) 1,3-dicyclohexylcarbodiimide (DCC) with a catalytic amount of 4-dimethylaminopyridine (DMAP),[19,20] and (ii) 2-chloro-1-methylpyridinium chlo-

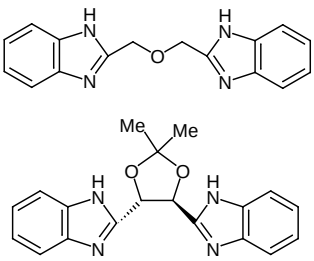


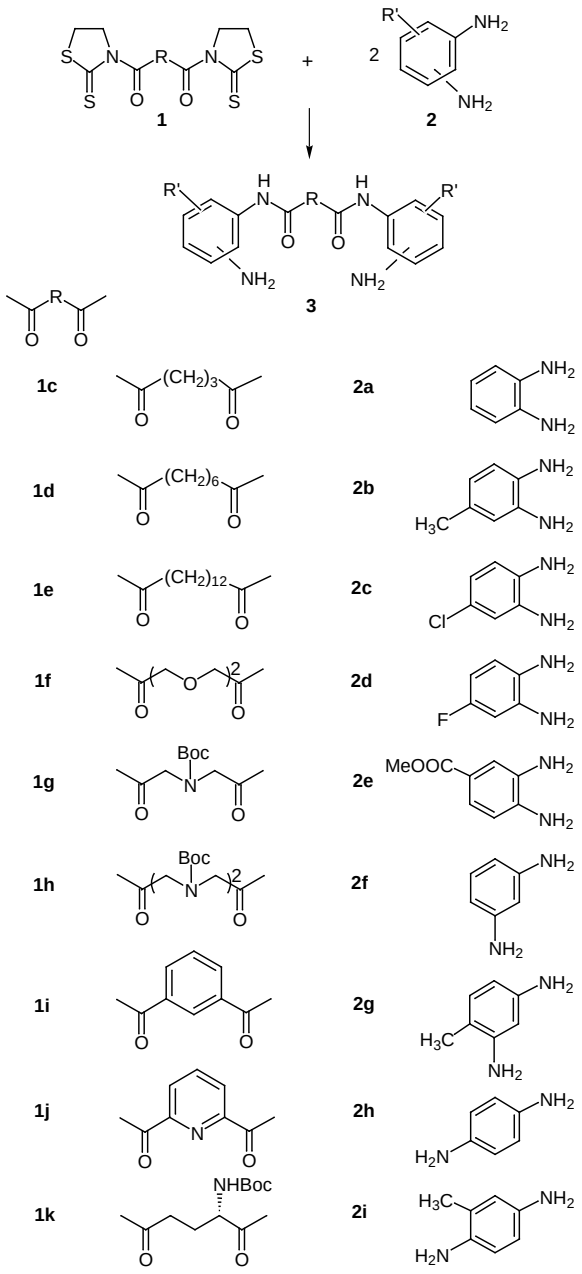
Figure Structures of bis(benzimidazolyl) derivatives isolated in the diamide diamine formation reaction via the hydroxysuccinimide route

ride,[21] or with the acid chloride in the presence of thalium(I) salt[19,20] or triethylamine.[22] Compounds **1c**–**k** were easily prepared by using the first and the last methods and were obtained in yields ranging from 58% to 99% depending on the reagent (acyl chloride route giving the best yields). These activated diacids were readily characterized by their yellow color and by their ^{1}H NMR spectra. As a matter of fact their formation was accompanied by a characteristic downfield shift of the CH_2N protons of the heterocyclic moiety ($\Delta\delta \approx 0.6$ ppm) as compared to the starting thiazolidine-2-thione ($\delta = 3.98$). Table 2 shows that these aliphatic or aromatic activated diacids gave the corresponding diamide diamines **3c**–**k** in moderate (52%) to high yields (92%). These yields may be improved by using larger amount of diamines. For instance, when the reactions were carried out with mercaptothiazolides **1a** or **1j** in the presence of three equivalents of diamine **2a**, compounds **3a** or **3j** were obtained in 93% and 75% yield, respectively, versus 80% and 57%, respectively, when two equivalents of diamine were used. One can note that this amidation reaction was also carried out with an amino acid residue (L-glutamic acid) and afforded compound **3k** in a good yield (Table 2, entry **k**). This result is in agreement with the successful application of mercaptothiazolide activation in peptide synthesis.[23]

As one can see from the other examples gathered in Table 2, the diamide diamines derived from substituted 1,2-diaminobenzenes were obtained in reasonable yields (entries **l**–**o**). For these acylation reactions an exclusive regioselectivity was observed, accordingly with the activating or deactivating nature of the substituent on the ring. A limitation of this method was found in acylation of 2,3-diaminonaphtalene. Owing to the less basic and less nucleophilic nature of this polyaromatic diamine, no reaction occurred in this experiment. This suggests that, with 1,2-diaminobenzene derivatives that are strongly deactivated, a more reactive diacid derivative is required to have access to the title compounds.

Our method is also applicable to other 1,n-diaminobenzenes under similar reaction conditions. When one equivalent of activated diacids **1a**,**i** was condensed with two equivalents of 1,3- or 1,4-diaminobenzene derivatives the corresponding diamide diamines were always the predominant products (Table 2, entries **p**–**u**). It is noteworthy that the compounds derived from 1,4-diaminobenzene, a core that is often used as a linker, were obtained with an excellent yield (>90%).

The structures proposed for new diamide diamine compounds **3** are consistent with data derived from infrared and nuclear magnetic resonance spectra in addition to satisfactory combustion analysis and molecular weights determined by mass spectrometry analyses (Table 3). Owing to the phenomenon of hindered internal rotation around the carbon–nitrogen bond of the amide group,[24] the presence of signals corresponding to the *trans* and *cis*



Scheme 2

forms would be expected in the ^{1}H and ^{13}C NMR spectra of these diamide compounds. With the exception of **3g**,**h**,**k**, compounds **3** showed a single resonance in NMR spectra for each chemically non-equivalent hydrogen or carbon. This suggested the existence of several rotamers in rapid interconversion (with respect to the time scale of NMR), or more certainly the presence of a single rotamer with N–H amide bond in the *trans* conformation.[24] On the contrary, the restricted rotation about the C–N bond of the carbamate group(s)[25] induced more complex NMR spectra for symmetrical compounds **3g** and **3h.**

Table 3 Spectroscopic Data for Diamide Diamines **3a**–**u**

Product	IR (KBr) ν (cm^{-1})	^{1}H NMR (200 MHz, DMSO-d_6)[a] δ, *J* (Hz)	^{13}C NMR (50.3 MHz, DMSO-d_6)[a] δ	MS *m*/*z* (%)
3a	3429, 3366, 3308 (NH_2, NH), 1679, 1653, 1612 (C=O)	4.27 (s, 4 H, CH_2), 4.94 (br s, 4 H, NH_2), 6.58 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 6.76 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 6.97 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 7.18 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 9.35 (s, 2 H, NH)	70.7 (CH_2), 115.8 (CH), 116.1 (CH), 122.2 (C–NH), 126.2 (CH), 126.5 (CH), 142.8 (C–NH_2), 167.9 (C=O)	315 (100) $[M + H]^+$
3b[b]	3446, 3380, 3343 (NH_2, NH), 1661 (C=O)	1.54 (s, 6 H, CH_3), 4.85 (s, 2 H, CH), 4.87 (br s, 4 H, NH_2), 6.59 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 6.76 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 6.97 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 7.20 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 9.37 (s, 2 H, NH)	26.3 (CH_3), 77.9 (CH), 112.1 [*C*(CH_3)$_2$], 115.8 (CH), 116.1 (CH), 122.2.(C–NH), 126.0 (CH), 126.6 (CH), 142.6 (C–NH_2), 167.8 (C=O)	371 (100) $[M + H]^+$
3c	3411, 3321, 3263 (NH_2, NH), 1642 (C=O)	1.92 (quint, 2 H, *J* = 7.3, CH_2), 2.41 (t, 4 H, *J* = 7.3, CH_2CO), 4.88 (br s, 4 H, NH_2), 6.54 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 6.73 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 6.90 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 7.19 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 9.13 (s, 2 H, NH)	21.4 (CH_2), 35.0 (CH_2), 115.8 (CH), 116.1 (CH), 123.4 (C–NH), 125.4 (CH), 125.7 (CH), 141.9 (C–NH_2), 170.8 (C=O)	313 (100) $[M + H]^+$
3d	3401, 3332, 3266 (NH_2, NH), 1642 (C=O)	1.37 (m, 4H, CH_2), 1.60 (m, 4H, CH_2), 2.33 (t, 4 H, *J* = 7.3, CH_2CO), 4.78 (br s, 4 H, NH_2), 6.54 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 6.72 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 6.90 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 7.17 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 9.04 (s, 2 H, NH)	25.2 (CH_2), 28.5 (CH_2), 35.7 (CH_2), 115.8 (CH), 116.1 (CH), 123.5 (C–NH), 125.2 (CH), 125.6 (CH), 141.8 (C–NH_2), 171.1 (C=O)	355 (100) $[M + H]^+$
3e	3428, 3345, 3286 (NH_2, NH), 1649 (C=O)	1.29 (m, 16 H, CH_2), 1.60 (m, 4 H, CH_2), 2.31 (t, 4 H, *J* = 7.3, CH_2CO), 4.80 (br s, 4 H, NH_2), 6.55 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 6.72 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 6.90 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 7.16 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 9.02 (s, 2 H, NH)	25.2 (CH_2), 28.6 (CH_2), 28.75 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 35.7 (CH_2), 115.8 (CH), 116.1 (CH), 123.5 (C–NH), 125.2 (CH), 125.6 (CH), 141.8 (C–NH_2), 171.1 (C=O)	439 (100) $[M + H]^+$
3f	3466, 3369, 3265 (NH_2, NH), 1657, 1621 (C=O)	3.80 (s, 4 H, CH_2), 4.15 (s, 4 H, CH_2CO), 4.78 (br s, 4 H, NH_2), 6.58 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 6.76 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 6.92 (td, 2 H, *J* = 8.0, 1.5, Ar-H), 7.22 (dd, 2 H, *J* = 8.0, 1.5, Ar-H), 8.97 (s, 2 H, NH)	70.1 (CH_2), 70.2 (CH_2), 116.0 (CH), 116.3 (CH), 122.7 (C–NH), 125.6 (CH), 126.1 (CH), 142.2 (C–NH_2), 168.1 (C=O)	359 (100) $[M + H]^+$
3g	3430, 3365, 3285 (NH_2, NH), 1685 (C=O, Boc), 1650 (C=O) amide)	1.40 (s, 9 H, CH_3), 4.13 (s, 4 H, CH_2), 4.85 (br s, 4 H, NH_2), 6.57 (m, 2 H, Ar-H), 6.72 (dd, 2 H, *J* = 7.4, 1.5, Ar-H), 6.93 (td, 2 H, *J* = 7.4, 1.5, Ar-H), 7.14 (m, 2 H, Ar-H), 9.80 (s, 2 H, NH)	27.8 (CH_3), 52.9, 53.2 (CH_2), 79.9 [*C*(CH_3)$_3$)] 115.4, 115.7, 115.8, 116.0 (CH), 122.2, 122.5 (C–NH), 125.2, 126.0, 126.1, 126.4 (CH), 142.1, 142.7 (C–NH_2), 154.7 (C=O, Boc), 168.8, 169.0 (C=O)	414 (100) $[M + H]^+$
3h	3434, 3359, 3274 (NH_2, NH), 1687 (C=O, Boc), 1631 (C=O, amide)	1.38, 1.44 (2 s, 18 H, CH_3), 3.42 (s, 4 H, CH_2N), 3.99 (s, 4 H, CH_2CO), 4.83 (br s, 4 H, NH_2), 6.55 (td, 2 H, *J* = 7.5, 1.5, Ar-H), 6.73 (dd, 2 H, *J* = 7.5, 1.5, Ar-H), 6.92 (td, 2 H, *J* = 7.5, 1.5, Ar-H), 7.14 (dd, 2 H, *J* = 7.5, 1.5, Ar-H), 9.15 (s, 2 H, NH)	27.9 (CH_3), 45.7, 46.1 (CH_2), 49.8, 50.5 (CH_2), 78.7, 78.9 [*C*(CH_3)$_3$], 115.5, 115.8, 116.1 (CH), 122.7, 123.0 (C–NH), 125.3, 125.7, 126.0 (CH), 142.1, 142.3 (C–NH_2), 154.8, 155.0 (C=O, Boc), 167.8 (C=O, amide)	557 (100) $[M + H]^+$
3i	3441, 3360, 3319 (NH_2, NH), 1655, 1625 (C=O)	4.97 (br s, 4 H, NH_2), 6.63 (td, 2 H, *J* = 7.8, 1.5, a.b.m.), 6.81 (dd, 2 H, *J* = 7.8, 1.5, a.b.m.), 7.01 (td, 2 H, *J* = 7.8, 1.5, a.b.m.), 7.22 (dd, 2 H, *J* = 7.8, 1.5, a.b.m.), 7.67 (t, 1 H, *J* = 7.7, i.m.), 8.17 (dd, 2 H, *J* = 7.7, 1.5, i.m.), 8.61 (t, 1 H, *J* = 1.5, i.m.), 9.80 (s, 2 H, NH)	116.0, 116.2 (CH, a.b.m.), 123.0 (C–NH), 126.6, 126.7 (CH, a.b.m.), 127.2, 128.3, 130.5 (CH, i.m.), 134.7 (C, i.m.), 143.1 (C–NH_2), 164.9 (C=O)	347 (100) $[M + H]^+$
3j	3387, 3333, 3260 (NH_2, NH), 1672 (C=O)	4.94 (br s, 4 H, NH_2), 6.65 (td, 2 H, *J* = 8.0, 1.5, a.b.m.), 6.84 (dd, 2 H, *J* = 8.0, 1.5, a.b.m.), 7.05 (td, 2 H, *J* = 8.0, 1.5, a.b.m.), 7.20 (dd, 2 H, *J* = 8.0, 1.5, a.b.m.), 8.22–8.38 (m, 3 H, py.m.), 10.67 (s, 2 H, NH)	115.8, 116.1 (CH, a.b.m.), 122.2 (C–NH), 124.7 (CH, py.m.), 127.2, 127.5 (CH, a.b.m.), 139.5 (CH, py.m.), 144.0 (C–NH_2), 148.8 (C, py.m.), 161.9 (C=O)	348 (100) $[M + H]^+$

Table 3 Spectroscopic Data for Diamide Diamines **3a**–**u** (continued)

Product	IR (KBr) ν (cm^{-1})	^{1}H NMR (200 MHz, DMSO-d_6)[a] δ, *J* (Hz)	^{13}C NMR (50.3 MHz, DMSO-d_6)[a] δ	MS *m*/*z* (%)
3k[c]	3432, 3374, 3307 (NH_2, NH), 1683 ((C=O, Boc) 1656,(C=O)	1.43 (s, 9 H, CH_3), 2.05 (m, 2 H, CH_2), 2.47 (m, 2 H, CH_2CO), 4.16 (m, 1 H, CH), 4.81 (br s, 4 H, NH_2), 6.56 (m, 2 H, Ar-H), 6.74 (m, 2 H, Ar-H), 6.92 (m, 3 H, Ar-H and NH-Boc), 7.20 (m, 2 H, Ar-H), 9.05, 9.12 (2 s, 2 H, NH)	27.6 (CH_2), 28.1 (CH_3), 32.2 (CH_2), 54.5 (CH), 78.2 [$C(CH_3)_3$], 115.5, 115.7, 116.0 (CH), 122.7, 123.3 (C–NH), 125.4, 125.7, 125.9, 126.2 (CH), 142.0, 142.5 (C–NH_2), 155.5 ((C=O, Boc), 170.5, 170.8 (C=O, amide)	428 (100) $[M + H]^+$
3l	3429, 3370, 3309 (NH_2, NH), 1678, 1649, 1617 (C=O)	2.18 (s, 6 H,CH_3), 4.24 (s, 4 H, CH_2), 4.77 (br s, 4 H, NH_2), 6.39 (dd, 2 H, *J* = 8.0, 1.7, Ar-$H_{5,5'}$), 6.57 (d, 2 H, *J* = 1.7, Ar-$H_{3,3'}$), 7.03 (d, 2 H, *J* = 8.0, Ar-$H_{6,6'}$), 9.27 (s, 2 H, NH)	20.8 (CH_3), 70.7 (CH_2), 116.2, 116.9 ($CH_{3,3'}$, $CH_{5,5'}$), 119.7 (C–NH), 126.2 ($CH_{6,6'}$), 135.5 ($C_{4,4'}$), 142.7 (C–NH_2), 167.8 (C=O)	343 (100) $[M + H]^+$
3m	3430, 3366, 3306 (NH_2, NH), 1677, 1649, 1614 (C=O)	4.26 (s, 4 H, CH_2), 5.20 (br s, 4 H, NH_2), 6.57 (dd, 2 H, *J* = 8.4, 2.4, Ar-$H_{5,5'}$), 6.79 (d, 2 H, *J* = 2.4, Ar-$H_{3,3'}$), 7.16 (d, 2 H, *J* = 8.4, Ar-$H_{6,6'}$), 9.33 (s, 2 H, NH)	70.6 (CH_2), 114.4, 115.2 ($CH_{3,3'}$, $CH_{5,5'}$), 120.9 (C–NH), 127.8 ($CH_{6,6'}$), 130.5 ($C_{4,4'}$), 144.5 (C–NH_2), 168.2 (C=O)	383 (100) $[M + H]^+$
3n	3438, 3366, 3315 (NH_2, NH), 1681, 1651, 1621 (C=O)	4.22 (s, 4 H, CH_2), 5.26 (br s, 4 H, NH_2), 6.33 (td, 2 H, *J* = 8.6, 2.9, Ar-$H_{5,5'}$), 6.50 (dd, 2 H, *J* = 11.2, 2.9, Ar-$H_{3,3'}$), 7.05 (dd, 2 H, *J* = 8.6, 6.3 Ar-$H_{6,6'}$), 9.32 (s, 2 H, NH)	70.6 (CH_2), 101.1 (d, *J* = 25.0, $CH_{3,3'}$), 101.8 (d, *J* = 23.0, $CH_{5,5'}$), 118.0 (C–NH), 128.4 (d, *J* = 10.5, $CH_{6,6'}$), 145.4 (d, *J* = 12.0, C–NH_2), 161.1 (d, *J* = 239.0, $C_{4,4'}$), 168.2 (C=O)	351 (100) $[M + H]^+$
3°	3428, 3337, 3287 (NH_2, NH), 1715 (C = O ester), 1669, 1632 (C=O)	3.76 (s, 6 H,CH_3), 4.28 (s, 4 H, CH_2), 5.77 (br s, 4 H, NH_2), 6.76 (d, 2 H, *J* = 8.5, Ar-$H_{3,3'}$), 7.58 (dd, 2 H, *J* = 8.5, 2.0, Ar-$H_{4,4'}$), 7.79 (d, 2 H, *J* = 2.0, Ar-$H_{6,6'}$), 9.34 (s, 2 H, NH)	54.1 (CH_3), 73.4 (CH_2), 117.0 ($CH_{3,3'}$), 118.7 ($C_{5,5'}$), 123.4 (C–NH), 131.3, 131.4 ($CH_{4,4'}$, $CH_{6,6'}$), 151.0 (C–NH_2), 168.8, 171.2 (C=O)	431 (52) $[M + H]^+$
3p	3432, 3345, 3308 (NH_2, NH), 1673, 1611 (C=O)	4.21 (s, 4 H, CH_2), 5.04 (br s, 4 H, NH_2), 6.32 (m, 2 H, Ar-H), 6.77 (m, 2 H, Ar-H), 6.96 (m, 4 H, Ar-H), 9.75 (s, 2 H, NH)	71.0 (CH_2), 105.2 (CH), 107.5 (CH), 109.7 (CH), 128.9 (CH), 138.8 (C–NH), 149.0 (C–NH_2), 167.7 (C=O)	315 (100) $[M + H]^+$
3q	3454, 3373, 3229 (NH_2, NH), 1636, 1621, 1607 (C=O)	5.13 (br s, 4 H, NH_2), 6.34 (m, 2 H, a.b.m.), 6.95 (m, 4 H, a.b.m.), 7.14 (t, 2 H, *J* = 2.0, a.b.m.), 7.66 (t, 1 H, *J* = 7.7, i.m.), 8.09 (dd, 2 H, *J* = 7.7, 1.6, i.m.), 8.45 (t, 1 H, *J* = 1.6, i.m.), 10.12 (s, 2 H, NH)	106.0, 108.3, 109.8 (CH, a.b.m.), 126.8, 128.4 (CH, i.m.), 128.8 (CH a.b.m.), 130.3 (CH, i.m.), 135.4 (C, i.m.), 139.6 (C–NH), 148.9 (C–NH_2), 164.8 (C=O)	364 (100) $[M + NH_4]^+$
3r	3457, 3364, 3281 (NH_2, NH), 1673 (C=O)	2.01 (s, 6 H, CH_3), 4.18 (s, 4 H, CH_2), 4.89 (br s, 4 H, NH_2), 6.72 (dd, 2 H, *J* = 8.0, 2.0, Ar-$H_{6,6'}$), 6.85 (d, 2 H, *J* = 8.0, Ar-$H_{5,5'}$), 7.01 (d, 2 H, *J* = 2.0, Ar-$H_{2,2'}$), 9.79 (s, 2 H, NH)	16.9 (CH_3), 71.0 (CH_2), 105.5, 107.9 ($CH_{2,2'}$, $CH_{6,6'}$), 116.7 ($C_{4,4'}$), 129.8 ($CH_{5,5'}$), 136.7 (C–NH), 146.6 (C–NH_2), 167.4 (C=O)	343 (100) $[M + H]^+$
3s	3437, 3348, 3310 (NH_2, NH), 1663 (C=O)	4.15 (s, 4 H, CH_2), 4.95 (br s, 4 H, NH_2), 6.53 (d, 4 H, *J* = 8.7, Ar-H), 7.26 (d, 4 H, *J* = 8.7, Ar-H), 9.70 (s, 2 H, NH)	70.9 (CH_2), 113.9 (CH), 121.7 (CH), 127.4 (C–NH), 144.8 (C–NH_2), 166.9 (C=O)	315 (100) $[M + H]^+$
3t	3463, 3363, 3319 (NH_2, NH), 1640 (C=O)	4.88 (br s, 4 H, NH_2), 6.58 (d, 4 H, *J* = 8.7, a.b.m.), 7.40 (d, 4 H, *J* = 8.7, a.b.m.), 7.62 (t, 1 H, *J* = 7.7, i.m.), 8.07 (dd, 2 H, *J* = 7.7, 1.6, i.m.), 8.46 (t, 1 H, *J* = 1.6, i.m.), 9.93 (s, 2 H, NH)	114.0, 122.0 (CH, a.b.m.), 126.5, 128.3 (CH, i.m.), 128.4 (C–NH), 130.0 (CH, i.m.), 135.3 (C, i.m.), 144.5 (C–NH_2), 164.2 (C=O)	364 (100) $[M + NH_4]^+$
3u	3411, 3384, 3289 (NH_2, NH), 1662 (C=O)	2.05 (s, 6 H, CH_3), 4.15 (s, 4 H, CH_2), 4.71 (br s, 4 H, NH_2), 6.57 (d, 2 H, *J* = 8.3, Ar-$H_{5,5'}$), 7.14 (dd, 2 H, *J* = 8.3, 2.4, Ar-$H_{6,6'}$), 7.19 (d, 2 H, *J* = 2.4, Ar-$H_{2,2'}$), 9.65 (s, 2 H, NH)	17.5 (CH_3), 70.8 (CH_2), 113.7 ($CH_{5,5'}$) 119.4 ($CH_{6,6'}$), 121.0 ($C_{3,3'}$), 122.8 ($CH_{2,2'}$), 127.3 (C–NH), 143.2 (C–NH_2), 166.8 (C=O)	343 (100) $[M + H]^+$

[a] Abbreviations used: a.b.m.: aminobenzene moiety, i.m.: isophtalic moiety, py.m.: pyridinyl moiety.
[b] $[\alpha]_D^{20}$ –21.3 (*c* = 1, DMSO).
[c] $[\alpha]_D^{20}$ +6.3 (*c* = 1, DMSO).

In conclusion, a two-step method was developed to prepare in good yields diamide diamines derived from 1,n-diaminobenzene compounds, which are important intermediates in organic synthesis. This method can be

carried out by a very simple procedure under mild and neutral conditions and is convenient for the preparation of large amounts of products. As a matter of fact, only stoichiometric equivalents of diamine and acylating agent are needed. The results presented here illustrate further the potential of thiazolidine-2-thione amide for mediating selective functional group transformation.[26]

Melting points were taken on a Kofler apparatus. ^{1}H (200 MHz) and ^{13}C (50.3 MHz) NMR spectra were recorded on a Bruker AC-200 spectrometer. IR spectra were determined with a Perkin-Elmer 883 spectrometer. Positive ES-MS spectra were performed with a Nermag R10–10C spectrometer using the Desorption Chemical Ionization (DCI/NH_3) technique. Optical rotations were measured with a Perkin Elmer 241 polarimeter. Elemental analyses were carried out by the "Service Commun de Microanalyse élémentaire UPS-INP" in Toulouse. Chromatographic purifications were performed by filtration through Merck silica gel (15 μm) or by column chromatography (Amicon silica gel 70–200 μm).

2,3-*O*-Isopropylidene-L-tartaric acid chloride was prepared as described previously.[14a] The other diacid dichlorides were synthesized from diacids using standard oxalyl chloride method. 1,4-Diaminobenzene, 2,5-diaminotoluene and 3,4-diaminotoluene were purified prior to use by recrystallization from benzene in the presence of activated carbon. 1,3-Thiazolidine-2-thione (2-mercaptothiazoline) was purchased from Lancaster Chemical Company, and used without further purification.

Bis(2-mercaptothiazolides) 1a–k; General Procedure

Method A: To a stirred solution of 1,3-thiazolidine-2-thione (15 mmol) and Et_3N (22 mmol) in anhyd THF (100 mL) was added dropwise the suitable diacid dichloride (7.5 mmol) in anhyd THF (30 mL) at 50 °C. The reaction mixture was stirred for 2 h, and then cooled to r.t. The triethylamine hydrochloride was filtered off and washed with THF. The filtrate was washed with 0.5 N NaOH solution (50 mL), then brine (50 mL) and dried (Na_2SO_4). After removal of the solvent, the yellow solid obtained was purified by filtration through a silica gel plug (CH_2Cl_2–acetone).

Method B: Dicyclohexylcarbodiimide (15 mmol) and a catalytic amount of 4-dimethylaminopyridine were added to a solution of the suitable diacid (7.5 mmol) and 1,3-thiazolidine-2-thione (15 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at r.t. for 24 h and the precipitate formed in the reaction was filtered off and washed with CH_2Cl_2. The filtrate was washed with 0.5 N NaOH solution (2 × 40 mL) then brine (2 × 40 mL), dried and concentrated in vacuo to give a yellow product, which was purified by filtration through a plug of silica gel (CH_2Cl_2–acetone).

The yields, physical and spectroscopic data of bis (2-mercaptothiazolide) **1a**–**k** are gathered in Table 4.

Table 4 Preparation and Spectroscopic Data for Bis(2-mercaptothiazolide) Derivatives **1a**–**k**

Product	Yield (%)[a] (Method)[b]	Mp (°C)[c]	IR ($CHCl_3$) $\nu_{C=O}$(cm^{-1})	^{1}H NMR (200 MHz,$CDCl_3$) δ, *J* (Hz)	^{13}C NMR (50.3 MHz, $CDCl_3$) δ
1a	95 (A) 76 (B)	145–147[d]	1710	3.38 (t, 4 H, *J* = 7.5, CH_2S), 4.61 (t, 4 H, *J* = 7.5, CH_2N), 5.12 (s, 4 H, CH_2O)	29.3 (CH_2S), 55.7 (CH_2N), 71.9 (CH_2O), 171.1 (C=O), 201.9 (C=S)
1b	60 (A)[e] 45 (B)[e]	not isolated	-	1.55 (s, 6 H, CH_3), 3.45 (m, 4 H, CH_2S), 4.55 (m, 4 H, CH_2N), 6.57 (s, 2 H, CH)	-
1c	97 (A)	94–95	1700	2.07 (quint, 2 H, *J* = 7.0, CH_2), 3.28 (t, 4 H, *J* = 7.5, CH_2S), 3.33 (t, 4 H, *J* = 7.0, CH_2CO), 4.57 (t, 4 H, *J* = 7.5, CH_2N)	19.9 (CH_2), 28.4 (CH_2S), 37.5 (*C*H_2CO), 56.1 (CH_2N), 174.1(C=O), 201.7 (C=S)
1d	87 (A)	109–110	1699	1.35 (m, 4 H, CH_2), 1.67 (m, 4H, CH_2), 3.22 (t, 4 H, *J* = 7.2, CH_2CO), 3.27 (t, 4 H, *J* = 7.5, CH_2S), 4.56 (t, 4 H, *J* = 7.5, CH_2N)	24.6 (CH_2), 28.4 (CH_2S), 28.8 (CH_2), 38.4 (*C*H_2CO), 56.1 (CH_2N), 174.8 (C=O), 201.6 (C=S)
1e	89 (A)	107–108[f]	1699	1.26 (m, 16 H, CH_2), 1.67 (m, 4 H, CH_2), 3.23 (t, 4 H, *J* = 7.2, CH_2CO), 3.26 (t, 4 H, *J* = 7.5, CH_2S), 4.56 (t, 4 H, *J* = 7.5, CH_2N)	24.8 (CH_2), 28.4 (CH_2S), 29.1, 29.4, 29.5, 29.6 (CH_2), 38.6 (*C*H_2CO), 56.1 (CH_2N), 175.0 (C=O), 201.6 (C=S)
1f	92 (A) 62 (B)	134–135	1710	3.37 (t, 4 H, *J* = 7.5, CH_2S), 3.80 (s, 4 H, CH_2O), 4.59 (t, 4 H, *J* = 7.5, CH_2N), 5.02 (s, 4 H, CH_2CO)	29.6 (CH_2S), 55.6 (CH_2N), 71.1, 73.6 (CH_2O), 171.9 (C=O), 201.2 (C=S)
1g	79 (B)	152–154	1706	1.42 (s, 9 H, CH_3), 3.35 (t, 4 H, *J* = 7.5, CH_2S), 4.57 (t, 4 H, *J* = 7.5, CH_2N), 4.91, 4.92 (2 s, 4 H, CH_2CO)	28.3 (CH_3), 29.4 (CH_2S), 54.9, 55.2, 55.8, 55.9 (*C*H_2CO, CH_2N), 81.1 (C-(CH_3)$_3$), 155.2 (C=O, Boc), 171.1 (C=O, amide), 201.5, 201.6 (C=S)
1h	76 (B)	197–200	1698	1.39, 1.46 (2 s, 18 H, CH_3), 3.34 (m, 8 H, CH_2S, C*H*$_2$NBoc), 4.57 (t, 4 H, *J* = 7.5, CH_2N), 4.83 (m, 4 H, CH_2CO)	28.3, 28.5 (CH_3), 29.3, 29.4 (CH_2S), 47.1, 47.4, 47.5 (*C*H_2NBoc), 54.8, 55.4, 55.5, 55.6, 55.9 (*C*H_2CO, CH_2N), 80.4, 80.6, 80.7 [*C*(CH_3)$_3$], 155.2, 155.5 (C=O, Boc), 171.3, 171.5 (C=O, amide), 201.4, 201.6 (C=S)

Table 4 Preparation and Spectroscopic Data for Bis(2-mercaptothiazolide) Derivatives **1a**–**k** (continued)

Product	Yield (%)[a] (Method)[b]	Mp (°C)[c]	IR ($CHCl_3$) $\nu_{C=O}$(cm^{-1})	^{1}H NMR (200 MHz,$CDCl_3$) δ, *J* (Hz)	^{13}C NMR (50.3 MHz, $CDCl_3$) δ
1i	91 (A)	98–100	1602	3.46 (t, 4 H, *J* = 7.4, CH_2S), 4.52 (t, 4 H, *J* = 7.4, CH_2N), 7.43 (t, 1 H, *J* = 7.8, Ar-H), 7.81 (dd, 2 H, *J* = 7.8, 1.7, Ar-H), 7.97(t, 1 H, *J* = 1.7, Ar-H)	29.9 (CH_2S), 56.5 (CH_2N), 128.4, 130.3, 133.1 (CH-Ar), 134.1 (C-Ar), 170.2 (C=O), 201.9 (C=S)
1j	99 (A)	104–105	1695	3.51 (t, 4 H, *J* = 7.5, CH_2S), 4.58 (t, 4 H, *J* = 7.5, CH_2N), 7.85 (m, 3 H, Ar-H)	30.6 (CH_2S), 56.2 (CH_2N), 126.5 (CH-Ar), 138.1 (CH-Ar), 151.1 (C-Ar), 168.3 (C=O), 201.9 (C=S))
1k[g]	58 (B)	170–172	1698	1.42 (s, 9 H, CH_3), 1.97, 2.32 (m, 2 H, CH_2), 3.38 (m, 6 H, CH_2S, CH_2CO), 4.56 (m, 4 H, CH_2N), 5.29 (m, 1 H, CH), 6.18 (m, 1 H, NH)	28.0 (CH_2), 28.4 (CH_3), 28.5, 28.6 (CH_2S), 34.8 (*C*H_2CO), 53.2 (CH), 56.1, 56.4 (CH_2N), 80.2 [*C*$(CH_3)_3$], 155.4(C=O, Boc), 173.9, 174.2 (C=O, amide), 201.3, 201.6 (C=S)

[a] Refers to isolated product unless otherwise noted.
[b] See experimental section.
[c] Solvent for recrystallization: EtOAc.
[d] Lit.[14d] mp 145–147 °C.
[e] Determined from ^{1}H NMR spectroscopy.
[f] Lit.[20b] mp 109–112 °C.
[g] $[\alpha]_D^{20}$ –26.9 (*c* = 1, $CHCl_3$).

Diamide Diamines 3a–u; General Procedure

To a stirred solution of 1,n-diaminobenzene derivative **2** (10 mmol) in CH_2Cl_2 (25 mL) was added dropwise a solution of bis(2-mercaptothiazolide) **1** (5 mmol) in CH_2Cl_2 (90 mL) at r.t. After the addition was complete (2 h), the mixture was allowed to stir until no further disappearance of yellowish color was observed (3–5 d).

Diamide diamines **3a**,**c**–**e**,**l**,**o**,**p**,**r**,**t**: were isolated by a simple filtration of the reaction mixture. The solid was washed with CH_2Cl_2 and dried in vacuo.

Diamide diamines **3b**,**f**–**h**,**j**,**n**,**u**: the reaction mixture was washed with 2 N NaOH solution (2 × 50 mL), brine (2 × 50 mL), and dried (Na_2SO_4). After the evaporation of the solvent under reduced pressure, the crude product was purified on a silica gel column using CH_2Cl_2–MeOH (95:05 for **3b**,**f**,**j**; 90:10 for **3h**), MeCN (**3n**) or MeCN–MeOH (95:05 for **3g**; 90:10 for **3u**) as eluent.

Diamide diamines **3i**,**k**,**m**,**q**,**s**: were isolated mainly by filtration. Additional product was obtained after aqueous workup of the filtrate as mentioned above and chromatography on a silica gel column using CH_2Cl_2–acetone (70:30) (**3i**), CH_2Cl_2–MeOH (90:10) (**3k**), CH_2Cl_2–acetone (70:30 → 50:50) (**3m**, **s**) or MeCN (**3q**) as eluent.

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